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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,634	CUSYATINER ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/28/03,11/14/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Swiss-Prot P43336*.

DETAILED ACTION

Status of the Application

Claims 1-7 are pending.

Applicant's election with traverse of Group I, claims 1-5 drawn to a transformed organism which produces L-valine, L-isoleucine, and L-homoleucine in an amount less than 1% of that of L-leucine, in a communication filed on 12/29/2005 is acknowledged.

Applicant's traverse is on the ground(s) that the Office has not provided reasons and/or examples to explain how Groups I-II are related as product and process of use. In addition, Applicants argue that the Office has not show that the proposed use of the claimed product is materially different from the claimed use. Furthermore, Applicants submit that the Office has not shown that there is a burden in searching the entire application, and indicate that upon a finding of allowability of the elected product claims, withdrawn process claims should be rejoined for examination.

Applicant's arguments have been fully considered but are not deemed persuasive to withdraw the restriction requirement. As required by MPEP § 806.05(h), the Examiner provided another method wherein the product of Group I can be used, i.e., in the production of compounds naturally found in that bacterial cell. Thus, in accordance with MPEP § 806.05(h), the Examiner has shown that the inventions are distinct. The *Escherichia* cell of Group I can be used, for example, to provide other amino acids not listed in the claims, as well as to provide proteins naturally found in *Escherichia* cells, such as endogenous enzymes. In addition, the *Escherichia* cell of Group I can be used, for example, to produce plasmid DNA. Therefore, it is clear that the product of Group I can have other uses besides that of Group II. With regard to arguments that the Examiner has not provided enough evidence to show that there is a burden in searching all inventions, it is noted that the Examiner indicated in item 3 of the restriction requirement reasons as to why it would be a burden to search the entire application. Specifically, the Examiner indicated that there is not only a separate classification but also that a comprehensive search of

all inventions would require at a minimum a separate patented/non-patented literature search and a separate class/subclass search which may not be co-extensive. Thus, in accordance with MPEP §803, the Examiner has prima facie shown why searching all the inventions would impose an undue burden on the Office. With regard to a rejoinder request, as indicated in the restriction requirement, items 4-5, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04.

The requirement is deemed proper and therefore is made FINAL.

Claims 6-7 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

1. The specification is objected to due to the presence of several grammatical/typographical errors. See, for example, "isoleucin" in Table 1, page 18, "absence of it's activity" in page 16, line 19, "modified gene encodes for a mutant enzyme...with undetectable by unknown methods level of its activity". Applicants are required to review the specification for additional errors and make the appropriate corrections without introducing new matter.

Priority

2. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to RUSSIAN FEDERATION application 2002116773 filed on 06/25/2002.

3. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. It is noted that the foreign priority document is in English.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 8/28/2003 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

5. The drawings submitted on 6/24/2003 have been reviewed and are approved by the Examiner.

Claim Objections

6. Claim 1 is objected to due to the recitation of "bacterium belonging to the genus *Escherichia*, which produces L-valine, L-isoleucine, and L-homoleucine in an amount of less than 1% of that of L-leucine produce". For clarity, it is suggested the term be amended to recite "bacterium belonging to the genus *Escherichia* which produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced" or similar. Appropriate correction is required.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim1 1-3, as written, do not sufficiently distinguish over bacterial cells as they exist naturally because the claim(s) does not particularly point out any non-naturally occurring differences between the claimed product and the naturally occurring product. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v.*

Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980). While claims 2-3 require an inactivated gene and/or increase/decrease of activity of a particular protein, the claims do not require those characteristics to be obtained by the intervention of the hand of man. Thus, cells with those characteristics can be naturally-occurring cells. The claim(s) should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" as taught by Example 1 (pages 15-17) of the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112, Second Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 3-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 3-4 (claim 5 dependent thereon) are indefinite in the recitation of "bacterium according to claim ....wherein the activity of the protein coded by tyrB gene is..." for the following reasons. As written, the term "tyrB" appears to be generic and not limited to a specific organism. While the gene nomenclature used may be appropriate for *Escherichia* species, the use of this nomenclature for genes encoding proteins of identical function in other organisms may not be accurate. As known in the art, genes encoding proteins of identical function in two different organisms may use different designations. In the instant case, the phhC gene of *P. aeruginosa* encodes an aromatic amino acid aminotransferase whereas the *E. coli* counterpart is the tyrB gene. See Swiss-Prot entry P43336 attached. As such, the use of gene terminology which is applicable to some organisms and not to others is confusing since the claims use this gene nomenclature with respect to any organism. For examination purposes, the term "tyrB gene" will be interpreted as "gene encoding an aromatic amino acid aminotransferase". If Applicants wish to use the term "tyrB" in the claims, it is suggested that the claims be amended to clearly indicate the organism associated with the specific gene designation used. Correction is required.

12. Claims 4-5 are under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. While the claims require transformation of the *Escherichia* cell with DNA containing the tyrB gene, there is no step correlating the transformation with the actual increase in protein activity. It is noted that transformation alone does not result in increased protein activity. The copy number of the DNA containing the tyrB gene needs to be increased for the corresponding protein to be produced in high amounts. For examination purposes, it will be assumed that claim 4 reads "the bacterium according to claim 3, wherein the aromatic amino acid aminotransferase activity is increased by transforming the bacterium with DNA encoding the aromatic amino acid aminotransferase, and increasing the copy number of the DNA encoding the aromatic amino acid transferase". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is directed to an *Escherichia* cell modified in <u>any</u> way such that it produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced. Claim 2 is directed to the *Escherichia* cell of claim 1 wherein the ilvE gene in said *Escherichia* cell is inactivated by <u>any</u> method, or the activity of the protein encoded by the ilvE gene in said *Escherichia* cell is reduced by <u>any</u> method.

Claim 3 is directed to the *Escherichia* cell of claim 2 wherein the activity of a genus of aromatic amino acid aminotransferases is increased by any method. Claims 4-5 are directed to the *Escherichia* cell of claim 3 wherein the activity of a genus of aromatic amino acid aminotransferases is increased by transforming said *Escherichia* cell with a genus of DNAs encoding aromatic amino acid aminotransferases, and increasing the copy number of said DNAs. See Claim Rejections under 35 USC §112, second paragraph for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The claims require an extremely large genus of genes encoding an aromatic amino acid aminotransferase and an extremely large genus of aromatic amino acid aminotransferases. In addition, the claims require (1) unknown methods to inactivate a gene, such as transcription inhibitors/regulators, or modifications in the regulatory region of a gene which would block transcription, and (2) unknown methods to decrease/increase the activity of a protein, such as mutations in the coding region of a gene

encoding the protein which would increase/decrease its activity, the addition of enhancers/inhibitors of that activity, or mutations in the regulatory region of a gene encoding said protein. While the specification and/or the art disclose the *E. coli* tyrB gene, inactivating deletions of the *E. coli* ilvE gene which would result in an inactive ilvE gene product, and increase in the activity of the *E. coli* tyrB gene product by overexpression of said gene, the specification fails to disclose the structure of other genes encoding other aromatic amino acid aminotransferases, other methods to inactivate a gene beyond an inactivating deletion, or other methods to increase/decrease the activity of a protein.

The claims require a genus of enzymes and a genus of DNAs encoding such enzymes which are structurally unrelated. A sufficient written description of a genus of enzymes/DNAs may be achieved by a recitation of a representative number of enzymes/DNAs defined by their amino acid/nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of enzymes/DNAs required in the claimed cell, and there is no information as to a correlation between the structures disclosed/known in the art and their required enzymatic activity. Furthermore, while one could argue that the structures of known aromatic amino acid aminotransferases and their corresponding DNAs are representative of all members of the genus of aromatic amino acid aminotransferases/DNAs required, such that the claimed invention is adequately described, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function,

and no additional information correlating structure with the enzymatic activity required has been provided, one cannot reasonably conclude that the known structures are representative of all the aromatic amino acid aminotransferases/DNAs required in the claimed invention.

Due to the fact that the specification only discloses (1) the *E. coli* tyrB gene and its product (aromatic amino acid aminotransferase), and (2) a single method to inactivate a gene and a single method to increase protein activity, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

15. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *Escherichia* cell wherein said cell produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced due to an inactivating deletion in the ilvE gene of said *Escherichia* cell, wherein the protein activity of the *E. coli* tyrB gene product is increased in said *Escherichia* cell by transforming said *Escherichia* cell with a DNA comprising the *E. coli* tyrB gene and increasing the copy number of the *E. coli* tyrB gene, does not reasonably provide enablement for an *Escherichia* cell modified in any way such that it produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced, an *Escherichia* cell wherein its ilvE gene is inactivated by any method, an *Escherichia* cell wherein the activity of the gene product of the ilvE gene is decreased by any method, an *Escherichia* cell wherein the activity of any aromatic amino acid aminotransferase is increased by any method, or an *Escherichia* cell transformed with any gene encoding an aromatic amino acid aminotransferase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 1-5 are so broad as to encompass (1) an *Escherichia* cell modified in any way such that it produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced, (2) an *Escherichia* cell wherein the ilvE gene in said *Escherichia* cell is inactivated by any method, or the activity of the protein encoded by the ilvE gene in said *Escherichia* cell is reduced by any method, (3) an *Escherichia* cell wherein the activity of any aromatic amino acid aminotransferase is increased by any method, (4) an *Escherichia* cell wherein the activity of any aromatic amino acid aminotransferase is increased by transforming said *Escherichia* cell with a DNA encoding any aromatic amino acid aminotransferase, and increasing the copy number of said DNA. See Claim Rejections under 35 USC §112, second paragraph for claim interpretation.

The enablement provided is not commensurate in scope with the claims due to the extremely large number of aromatic amino acid aminotransferases and genes encoding those aminotransferases for which there is no structure disclosed, as well as the unknown methods which would allow (1) an *Escherichia* cell to produce L-leucine, L-valine, L-isoleucine, and L-homoleucine, wherein the amount of L-valine, L-isoleucine, and L-homoleucine is less than 1% the amount of L-leucine produced (2) inactivation of the ilvE gene from an *Escherichia* cell, (3) reduction of activity of an *Escherichia* ilvE gene product in an *Escherichia* cell, and (4) increase of activity of any aromatic amino acid

aminotransferase. In the instant case, the specification enables an *Escherichia* cell wherein said cell produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced due to an inactivating deletion in the ilvE gene of said *Escherichia* cell, wherein the protein activity of the *E. coli* tyrB gene product is increased in said *Escherichia* cell by transforming said *Escherichia* cell with a DNA comprising the *E. coli* tyrB gene and increasing the copy number of the *E. coli* tyrB gene.

The amount of direction or guidance presented and the existence of working examples. The specification discloses a mutant *E. coli* cell which has an inactivating deletion in the ilvE gene (strain 505) which has been transformed with a multicopy vector containing the *E. coli* tyrB gene, wherein the copy number of the *E. coli* tyrB gene is increased, as a working example. However, the specification fails to disclose (1) other methods to obtain an *Escherichia* cell which would produce L-leucine, L-valine, L-isoleucine, and L-homoleucine, wherein the amount of L-valine, L-isoleucine, and L-homoleucine is less than 1% the amount of L-leucine produced, (2) the structures of other genes encoding any aromatic amino acid aminotransferase, and (3) other methods to (i) inactivate an *Escherichia* ilvE gene, (ii) reduce the activity of any *Escherichia* ilvE gene product, or (iii) increase the activity of any aromatic amino acid aminotransferase.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The amino acid sequence of a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and any aromatic amino acid aminotransferase such that one of skill in the art can envision the structure of <u>any</u> aromatic amino acid aminotransferase, or its corresponding coding polynucleotide. In addition, the art does not provide any teaching or guidance as to how the structures of those aromatic amino acid aminotransferases known in the art correlate with that enzymatic activity. The art clearly teaches that structural changes in a protein to obtain the desired activity without any

guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a protein were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all enzymes having aromatic amino acid aminotransferase activity, or to screen for an essentially infinite number of mutations either in the regulatory region of a gene or in the coding region of a gene to determine which ones result in either an aromatic amino acid aminotransferase with higher enzymatic activity per molecule, or increased amount of said aminotransferase per cell. Furthermore, while there is a limited number of methods known in the art which would inactivate any gene (e.g., deletions), it is not routine in the art to screen by trial and error for (1) any modification which would lead to the specific inactivation of an *Escherichia* ilvE gene, such as any number of mutations in the regulatory region of that gene blocking transcription, or the expression/addition of any number of transcription inhibitors/regulators, or (2) an essentially infinite number of mutations either in the regulatory region of

an *Escherichia* ilvE gene, or in the coding region of such gene, to determine which ones result in either lower enzymatic activity of the ilvE gene product per molecule, or decreased amount of said gene product per cell. In the absence of (1) a correlation between structure and the required enzymatic activity, (2) some guidance as to the structural changes required in any aromatic amino acid aminotransferase or any *Escherichia* ilvE gene product which would result in a decrease/increase of their enzymatic activity, (3) some guidance as to the structural changes required in the regulatory elements of any *Escherichia* ilvE gene or any gene encoding an aromatic amino acid aminotransferase such that the production of the gene products can be modulated, (4) some guidance as to the structure of modulators (enhancers/inhibitors) of the required enzymatic activity, and (5) some guidance as to the structural modifications required in any *Escherichia* ilvE gene to inactivate such gene, or the structure of molecules capable of inactivating such gene, one of skill in the art would have to test an essentially infinite number of proteins to determine which ones have aromatic amino acid aminotransferase activity, and test an essentially infinite number of modifications to determine which ones would inactivate any *Escherichia* ilvE gene, and which ones would increase/decrease the activity of any aromatic amino acid aminotransferase or any *Escherichia* ilvE gene product.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Gelfand et al. (J. Bacteriol. 130(1):429-440; cited in the IDS).

Claims 1-2 are directed in part to an *Escherichia* cell which produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced due to the inactivation of the ilvE gene in said *Escherichia* cell.

Gelfand et al. teach two mutant *E. coli* cells which can synthesize leucine, wherein the ilvE gene has an inactivating deletion, DG31 ($ilvE^-$ $tyrB^+$) and DG34 ($ilvE^-$ $tyrB^+$), and the endogenous tyrB gene is functional (page 436, right column, Leucine biosynthesis by the tyrB aminotransferase, page 437 left column). Gelfand et al. also teach that the presence of the tyrB gene product (aromatic amino acid aminotransferase) allows leucine to be synthesized (DG31 and DG34 can grow in the absence of leucine) whereas its absence results in not enough leucine to sustain growth (strain DG27 ($ilvE^-$ $tyrB^-$) has an absolute requirement for leucine). The specification discloses that an inactivating deletion in the ilvE gene of an *E. coli* cell (strain 505; tyrB gene remains functional) results in that *E. coli* cell to produce leucine at higher amounts than valine, isoleucine and homoleucine (Table 1). The amount of valine, isoleucine and homoleucine produced by strain 505 is less than 1% the amount of leucine produced (Table 1, second entry). Therefore, in the absence of evidence to the contrary, it appears that an inactivating deletion of the ilvE gene in an *E. coli* cell, wherein the tyrB gene in that *E. coli* cell remains functional, would be sufficient for that cell to produce leucine and produce valine, isoleucine, and

homoleucine at amounts which are less than 1% those of leucine. Thus, the *E. coli* mutants of Gelfand et al. would be expected to produce valine, isoleucine, and homoleucine at amounts which are less than 1% the amount of leucine produced by the *E. coli* mutants Therefore, the *E. coli* mutants of Gelfand et al. anticipate the instant claims as written.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al. (J. Bacteriol. 130(1):429-440; cited in the IDS). The teachings of Gelfand et al. have been described above. Gelfand et al. does not teach (1) transformation of the *E. coli* mutants with DNA encoding the *E. coli* tyrB gene product using a multicopy vector, or (2) increase in the activity of the *E. coli* tyrB gene product by virtue of increasing the copy number of said DNA.

Claims 3-5 are directed in part to the *Escherichia* cell of claim 2 as described above, wherein the activity of an aromatic amino acid aminotransferase is increased by transforming said *Escherichia* cell

with a multicopy vector comprising a DNA encoding said aromatic amino acid aminotransferase, and increasing the copy number of said DNA. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to transform the *E. coli* mutants of Gelfand et al. with a multicopy vector, wherein said vector comprises a DNA encoding the *E. coli* tyrB gene product (aromatic amino acid aminotransferase) to increase the copy number of said DNA and produce more of the tyrB gene product (an increase in the production of the tyrB gene product in active form would result in increased activity). A person of ordinary skill in the art is motivated to transform the *E. coli* mutants of Gelfand et al. with a multicopy vector comprising DNA encoding the tyrB gene product to (1) produce leucine, which is an amino acid of industrial importance, while reducing the amount of other amino acids, and (2) to further characterize the leucine/valine/isoleucine biosynthetic pathway. As indicated above, Gelfand et al. teach that the presence of the tyrB gene product results in leucine synthesis. In addition, *E. coli* is a well known microbial producer of amino acids. One of ordinary skill in the art has a reasonable expectation of success at transforming the *E. coli* mutants of Gelfand et al. with a multicopy vector comprising the *E. coli* tyrB gene since transformation of *E. coli* cells with multicopy number vectors is well known and widely used in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

21. No claim is in condition for allowance.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
March 14, 2006